PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 15/25, C07K 14/545, C12N 15/63, 5/10, C07K 19/00, 16/24

A2

(11) International Publication Number: WO 00/39297

(43) International Publication Date: 6 July 2000 (06.07.00)

(21) International Application Number: PCT/US99/30720

(22) International Filing Date: 22 December 1999 (22.12.99)

(30) Priority Data:

60/113,430	23 December 1998 (23.12.98)	US
60/116,843	22 January 1999 (22.01.99)	US
60/129,122	13 April 1999 (13.04.99)	US

(71) Applicant *(for all designated States except US)*: GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080–4990 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: GODDARD, Audrey [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). PAN, James [CA/US]; 2705 Coronet Boulevard, Belmont, CA 94002 (US).

(74) Agents: LOVE, Richard, B. et al.; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080–4990 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: IL–1 RELATED POLYPEPTIDES

(57) Abstract

The present invention is directed to novel polypeptides having homology to the IL–1–like family of proteins and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention, and methods for producing the polypeptides of the present invention.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

In yet another embodiment, the invention concerns agonists and antagonists of a native IL-1lp polypeptide. In a particular embodiment, the agonist or antagonist is an anti-IL-1lp antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native IL-1lp polypeptide, by contacting the native IL-1lp polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising an IL-1lp polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) and derived amino acid sequences (SEQ ID NOS:2-3) related to a native sequence hIL-1Ra1. The nucleotide sequence (SEQ ID NO:1) contains an intron believed to extend from nucleotide positions 181 to 432, with a splice donor site at nucleotide positions 181 to 186 and splice acceptor site at nucleotide positions 430 to 432. The amino acid sequences (SEQ ID NOS:2 and 3) are derived from the exonic sequences that are believed to make up the processed (intron-free) coding sequence.

Figure 2 shows the nucleotide sequence (SEQ ID NO:4) and derived amino acid sequence (SEQ ID NO:5) of a native sequence hIL-1Ra1 polypeptide fused at its N-terminus to a heterologous signal peptide (amino acid positions 1-15), flag peptide affinity handle (amino acid positions 16-23) and peptide linker (amino acid positions 24-36).

Figure 3 shows the nucleotide sequence (SEQ ID NO:6) and derived amino acid sequence (SEQ ID NO:7) of a native sequence hIL-1Ra1 polypeptide. The nucleotide sequence (SEQ ID NO:6) and derived amino acid sequence (SEQ ID NO:7) are believed to represent the processed (intron-free) form and intact hIL-1Ra1 polypeptide, respectively, of the nucleotide sequence (SEQ ID NO:1) and amino acid sequences (SEQ ID NOS:2-3) of Figure 1. The start and stop codons in the coding sequence are located at nucleotide positions 103-105 and 682-684, respectively. The putative signal sequence extends from amino acid positions 1 to 14. A putative cAMP- and cGMP-dependent protein kinase phosphorylation site is located at amino acid positions 33-36. Putative N-myristoylation sites are located at amino acid positions 50-55 and 87-92.

Figure 4 shows the nucleotide sequence (SEQ ID NO:8) of EST AI014548.

Figure 5 shows the nucleotide sequence (SEQ ID NO:9) and derived amino acid sequence (SEQ ID NO:10) of a native sequence hIL-1Ra2 polypeptide. The start and stop codons in the coding sequence are located at nucleotide positions 96-98 and 498-500, respectively. The putative signal sequence extends from amino acid positions 1-26.

Figure 6 shows the nucleotide sequence (SEQ ID NO:11) of EST 1433156.

Figure 7 shows the nucleotide sequence (SEQ ID NO:12) and derived amino acid sequence (SEQ ID NO:13) of a native sequence hIL-1Ra3 polypeptide. The start and stop codons in the coding sequence are located at nucleotide positions 1-3 and 466-468, respectively. The putative signal sequence extends from amino acid positions 1-33. Putative N-myristoylation sites are located at amino acid positions 29-34, 30-35, 60-65, 63-68, 73-78, 91-96 and 106-111. An interleukin-1-like sequence is located at amino acid positions 111-131.

In another embodiment, the invention provides a method for treating an hIL-1Ra1-mediated graft-versus-host disease (GVHD) comprising administering to a human in need of such treatment an effective amount of an anti-hIL-1Ra1 antibody.

In another embodiment, the invention provides a method for treating an IL-1lp-mediated inflammatory bowel disease such as ulcerative colitis, comprising administering to a mammal, such as human, in need of such treatment an effective amount of an anti-IL-1lp antibody.

In another embodiment, the invention provides a method for treating an hIL-1lp-mediated inflammatory bowel disease such as ulcerative colitis, comprising administering to a human in need of such treatment an effective amount of an anti-hIL-1lp antibody.

In another embodiment, the invention provides a method for treating an hIL-1Ra1-mediated inflammatory bowel disease such as ulcerative colitis, comprising administering to a human in need of such treatment an effective amount of an anti-hIL-1Ra1 antibody.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

EXAMPLE 1

Isolation of DNA encoding hIL-1Ra1 and mIL-1Ra3

A public expressed sequence tag (EST) DNA database (Genbank) was searched with human interleukin-1 receptor antagonist (hIL-1Ra) sequence, also known as secretory human interleukin-1 receptor antagonist ("sIL-1Ra") sequence, and a human EST designated AI014548 (Figure 4, SEQ ID NO:8), and a murine EST designated W08205 (Figure 10, SEQ ID NO:17), were identified, which showed homology with the known protein hIL-1Ra (sIL-1Ra).

EST clones AI014548 and W08205 were purchased from Research Genetics (Huntsville,AL) and the cDNA inserts were obtained and sequenced in their entireties.

The entire nucleotide sequence of the clone AI014548, designated DNA85066, is shown in Figure 1 (SEQ ID NO:1). Clone DNA85066 contains a single open reading frame that is interrupted by an apparent intronic sequence. The intron is bounded by splice junctions at nucleotide positions 181 to 186 (splice donor site) and nucleotide positions 430 to 432 (splice acceptor site) (Fig.1; SEQ ID NO:1).

A virtual processed nucleotide sequence (Fig. 3; SEQ ID NO:6), designated DNA94618, was derived by removing the apparent intronic sequence from clone DNA85066. Clone DNA94618 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 103-105, and a stop codon at nucleotide positions 682-684 (Fig. 3; SEQ ID NO:6). The predicted polypeptide precursor (hIL-1Ra1) (Fig. 3; SEQ ID NO:7) is 193 amino acids long. The putative signal sequence extends from amino acid positions 1 to 14. A putative

cAMP- and cGMP-dependent protein kinase phosphorylation site is located at amino acid positions 33-36. Putative N-myristoylation sites are located at amino acid positions 50-55 and 87-92.

Clone DNA85066 (designated as DNA85066-2534) has been deposited with ATCC and was assigned ATCC deposit no. 203588. The full-length hIL-1Ra1 protein shown in Figure 3 (SEQ ID NO:7) has an estimated molecular weight of about 21,822 daltons and a pI of about 8.9.

Based on a sequence alignment analysis of the full-length sequence (SEQ ID NO:7), hIL-1Ra1 shows significant amino acid sequence identity to hIL-1Ra (sIL-1Ra) and hIL-1Raβ proteins.

The entire nucleotide sequence of the clone W08205, designated DNA92505, is shown in Figure 9 (SEQ ID NO:15). Clone DNA92505 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 145-147, and a stop codon at nucleotide positions 610-612 (Fig. 9; SEQ ID NO:15). The predicted polypeptide precursor (mIL-1Ra3) (Fig. 9; SEQ ID NO:16) is 155 amino acids long. The putative signal sequence extends from amino acid positions 1-33. Putative N-myristoylation sites are located at amino acid positions 29-34, 60-65, 63-68, 91-96 and 106-111. An interleukin-1-like sequence is located at amino acid positions 111-131.

Clone DNA92505 (designated as DNA92505-2534) was deposited with ATCC and was assigned ATCC deposit no. 203590. The full length mIL-1Ra3 protein shown in Figure 9 (SEQ ID NO:16) has an estimated molecular weight of about 17,134 daltons and a pI of about 4.8.

Based on a sequence alignment analysis of the full-length sequence (SEQ ID NO:16), mIL-1Ra3 shows significant amino acid sequence identity to mIL-1Ra, hicIL-1Ra, hIL-1Ra (sIL-1Ra) and hIL-1Raβ proteins.

EXAMPLE 2

Isolation of DNA encoding hIL-1ra2 and hIL-1Ra3

A expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched with human interleukin-1 receptor antagonist (hIL-1Ra) sequence, also known as secretory human interleukin-1 receptor antagonist ("sIL-1Ra") sequence, and the ESTs, designated 1433156 (Figure 5, SEQ ID NO:9) and 5120028 (Figure 7, SEQ ID NO:12), were identified, which showed homology with the hIL-1Ra known protein.

EST clones 1433156 and 5120028 were purchased from Incyte Pharmaceuticals (Palo Alto, CA) and the cDNA inserts were obtained and sequenced in their entireties.

The entire nucleotide sequence of the clone 1433156, designated DNA92929, is shown in Figure 5 (SEQ ID NO:9). Clone DNA92929 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 96-98, and a stop codon at nucleotide positions 498-500 (Fig. 5; SEQ ID NO:9). The predicted polypeptide precursor (hIL-1Ra2) (Fig. 5; SEQ ID NO:10) is 134 amino acids long. A putative signal sequence extends from amino acid positions 1-26.

Clone DNA92929 (designated as DNA92929-2534) was deposited with ATCC and was assigned ATCC deposit no. 203586. The full-length hIL-1Ra2 protein shown in Figure 5 (SEQ ID NO:10) has an estimated molecular weight of about 14,927 daltons and a pI of about 4.8.

081.mit.edu/GENESCAN.html). The ORF-encoding sequence was used to design two DNA primers, ggc gga tcc aaa atg ggc tct gag gac tgg g (SEQ ID NO:29) (1Ra1016) and gcg gaa ttc taa tcg ctg acc tca ctg ggg (SEQ ID NO:30) (1Ra1017). The 1Ra1016 and 1Ra1017 primers were synthesized and used to clone cDNA from human fetal skin and SK-lu-1 cell cDNA libraries using polymerase chain reaction (PCR). Several PCR products were isolated and sequenced. Two full length cDNA clones (designated DNA102043 and DNA102044) from PCR products were found to encode hIL-1Ra1 isoforms.

The entire nucleotide sequence of clone DNA102043 is shown in Figure 15 (SEQ ID NO:18). Clone DNA102043 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 4-6, and a stop codon at nucleotide positions 625-627 (Figure 15; SEQ ID NO:18). The predicted polypeptide precursor (designated hIL-1Ra1L) (Fig. 15; SEQ ID NO:19) is 207 amino acids long. The putative signal sequence extends from amino acid positions 1-34.

Clone DNA102043 (designated DNA102043-2534) was deposited with ATCC and was assigned ATCC deposit no. 203846. The full-length hIL-1Ra1L protein shown in Figure 15 (SEQ ID NO:19) has an estimated molecular weight of about 23,000 daltons and a pI of about 6.08.

Based on a sequence alignment analysis of the full length sequence (SEQ ID NO:19), hIL-1Ra1L shows significant amino acid sequence identity to hIL-1Raβ and TANGO-77 protein. In addition, a portion of the DNA sequence of clone DNA102043 (Figure 15) (SEQ ID NO:18) was found to coincide with the DNA sequence of EST AI014548 (Figure 4) (SEQ ID NO:8) and with the complement of the DNA sequence of EST AI323258 (Figure 17) (SEQ ID NO:23).

The entire nucleotide sequence of clone DNA102044 is shown in Figure 16 (SEQ ID NO:20). Clone DNA102044 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 4-6, and a stop codon at nucleotide positions 505-507 (Figure 16; SEQ ID NO:20). The predicted polypeptide (designated hIL-1Ra1S) (Fig. 16; SEQ ID NO:21) is 167 amino acids long, and it is believed to behave as a mature sequence (without a presequence that is removed in post-translational processing) in certain animal cells. In addition, it is believed that other animal cells recognize and remove in post-translational processing one or more signal peptide(s) contained in the sequence extending from amino acid positions 1 to about 46.

Clone DNA102044 (designated DNA102044-2534) was deposited with ATCC and was assigned ATCC deposit no. 203855. The full-length hIL-1Ra1S protein shown in Figure 16 (SEQ ID NO:21) has an estimated molecular weight of about 18,478 daltons and a pI of about 5.5.

Based on a sequence alignment analysis of the full length sequence (SEQ ID NO:21), hIL-1Ra1S appears to be an allelic variant of TANGO-77 protein and also shows significant amino acid sequence identity to hIL-1Raβ. In addition, a portion of the DNA sequence of clone DNA102044 (Figure 16) (SEQ ID NO:20) was found to coincide with the DNA sequence of EST AI014548 (Figure 4) (SEQ ID NO:8) and with the complement of the DNA sequence of EST AI323258 (Figure 17) (SEQ ID NO:23).

EST clone AI323258 was purchased from Research Genetics (Huntsville, AL) and the cDNA insert was obtained and sequenced in its entirety. The entire sequence of the clone

AI323258, designated DNA114876, is shown in Figure 19 (SEQ ID NO:24). Clone DNA114876 contains a single open reading frame (ORF) with an apparent translation initiation site at nucleotide positions 73-75 and a stop codon at nucleotide positions 726-728 (Figure 19; SEQ ID NO:24), encoding a predicted polypeptide precursor (hIL-1Ra1V) (Fig. 19; SEQ ID NO:25) that is 218 amino acids long. In addition, the ORF contains an alternate translation initiation site at nucleotide positions 106-108. The predicted polypeptide (also designated hIL-1Ra1V) for translation initiated at the alternate start codon is 207 amino acids in length (lacking the first eleven residues at the N-terminus of the 218 amino acid polypeptide). It is believed that the predicted 218 amino acid and 207 amino acid polypeptides behave as mature sequences (without a presequence that is removed in post-translational processing) in certain animal cells. It is also believed that other animal cells recognize and remove one or more signal peptide(s) extending from amino acid positions 1 to about 48 (a putative leader sequence in the 218 amino acid polypeptide) or from amino acid positions 12 to 36 (a putative leader sequence in the 207 amino acid polypeptide) in the amino acid sequence of Figure 19 (SEQ ID NO:25). As shown in Example 14 below, transiently transfected CHO host cells secrete unprocessed forms of hIL-1Ra1V and hIL-1Ra1L and a single processed form that results from the removal of a signal peptide extending from amino acid positions 1 to 45 in Figure 19 (SEQ ID NO:25) or the removal of a signal peptide extending from amino acid positions 1 to 34 of Figure 15 (SEQ ID NO:19). The processed form of hIL-1Ra1V and hIL-1Ra1L secreted by transiently transfected CHO host cells has the amino acid sequence of amino acid residues 35 to 207 of Figure 15 (SEQ ID NO:19) and amino acid residues 46 to 218 of Figure 19 (SEQ ID NO:25).

Clone DNA114876 (designated DNA114876-2534) was deposited with ATCC and was assigned ATCC deposit no. 203973. The full length hIL-1Ra1V protein shown in Figure 19 (SEQ ID NO:25) has an estimated molecular weight of about 24,124 and a pI of about 6.1.

Based on a sequence alignment analysis of the full length sequence (SEQ ID NO:25), hIL-1Ra1V shows significant amino acid sequence identity to hIL-1Raβ. hIL-1Ra1V is believed to be an allelic variant of hIL-1Ra1L.

EXAMPLE 13

IL-18 Receptor and IL-1Receptor Binding of hIL-1Ra1S

To facilitate the characterization of hIL-1Ra1S, a PCR fragment encoding amino acid residues 39-167 in the ORF of clone DNA102044 (Figure 16; SEQ ID NO:21) was cloned into pCMV1FLAG (IBI Kodak, described in Pan et al., Science, 276: 111-113) as an in-frame fusion to a NH_2-terminal preprotrypsin leader sequence and FLAG tag encoded by the vector to form plasmid pCMV1FLAG-IL-1Ra1S. Plasmid pCMV1FLAG-IL18R-ECD-Fc was obtained as described in Example 9 above.

Human embryonic kidney 293 cells were grown in high glucose DMEM (Genentech, Inc). The cells were seeded at 3-4 $X10^6$ per plate (100 mm) and co-transfected with pCMV1FLAG-hIL-1Ra1S and pCMV1FLAG-IL18R-ECD-Fc by means of calcium phosphate precipitation. The media were changed 12 hours post transfection. The resultant conditioned media (10 ml each) were harvested after a further 70-74 hour incubation, clarified by centrifugation, aliquoted and stored at -70°C. The receptor-Fc and ligand complex from 1.5 ml conditioned medium was

unprocessed N-terminus, indicating that the CHO host cells also secreted unprocessed forms of hIL-1Ra1L and hIL-1Ra1V corresponding to amino acid residues 1 to 207 in the amino acid sequence of Figure 15 (SEQ ID NO:19) and to amino acid residues 1 to 218 in the amino acid sequence of Figure 19 (SEQ ID NO:25), respectively.

The processed N-terminal sequence of both of the hIL-1Ra3 and mIL-1Ra3 polypeptides was determined to be VLSGALCFRM (SEQ ID NO:33). Approximately 100% of the hIL-1Ra3 and mIL-1Ra3 material recovered from conditioned media exhibited the processed N-terminal sequence, indicating that the CHO host cells secreted processed forms of hIL-1Ra3 and mIL-1Ra3 that lack the N-terminal methionine and correspond to amino acid residues 2 to 155 in the amino acid sequence of Figure 7 (SEQ ID NO:13) and amino acid residues 2 to 155 in the amino acid sequence of Figure 9 (SEQ ID NO:16), respectively.

Deposit of Material

The following materials have been deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC):

Material	ATCC Dep. No.	Deposit Date
pSPORT1-based plasmid DNA92929-2534	203586	Jan. 12,1999
pCMV-1Flag-pcmv5 plasmid DNA96786-2534	203587	Jan. 12, 1999
pT7T3D-Pac plasmid DNA85066-2534	203588	Jan. 12, 1999
pINCY-based plasmid DNA96787-2534	203589	Jan. 12, 1999
pT7T3D-Pac plasmid DNA92505-2534	203590	Jan. 12, 1999
pRK7-based plasmid DNA102043-2534	203846	March 16, 1999
pRK7-based plasmid DNA102044-2534	203855	March 16, 1999
pRK7-based plasmid DNA114876-2534	203973	April 27, 1999

These deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of viable cultures of the deposits for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the cultures of the deposits to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 24 August 2000 (24.08.00)	
International application No. PCT/US99/30720	**Applicant's or agent's file reference** P2534-3
International filing date (day/month/year) 22 December 1999 (22.12.99)	**Priority date** (day/month/year) 23 December 1998 (23.12.98)
Applicant GODDARD, Audrey et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

21 July 2000 (21.07.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Charlotte ENGER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Articl 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
P2534-3		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/30720	22/12/1999	23/12/1998
Applicant		
GENENTECH, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERI ONAL SEARCH REPORT

Int[redacted]onal Application No
PCT/US 99/30720

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/25 C07K14/545 C12N15/63 C12N5/10 C07K19/00
C07K16/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DINARELLO C. A. ET AL.: "Induction of Interleukin-1 and Interleukin-1 Receptor Antagonist" SEMINARS IN ONCOLOGY, vol. 24, no. 3, Suppl. 9, June 1997 (1997-06), pages S9-81-S9-93, XP000864695 page S9-83, column 2, line 25 -page S9-85, column 1, line 23 ---	1,2,7,8, 12,14, 16-18, 20,22, 25-30
P,X	WO 99 06426 A (MILLENNIUM BIOTHERAPEUTICS INC) 11 February 1999 (1999-02-11) figure 1 --- -/--	1,2,7,8, 14, 16-18, 20,22, 25-30

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 2000	19. 10. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schönwasser, D

4

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 24899 A (ZYMOGENETICS INC) 4 May 2000 (2000-05-04) SEQ ID NO:1; SEQ ID NO:1 --- WO 00 17363 A (SCHERING CORP) 30 March 2000 (2000-03-30) SEQ ID NO:3, SEQ ID NO:4 --- WO 00 36108 A (IMMUNEX CORP) 22 June 2000 (2000-06-22) SEQ ID NO:1, SEQ ID NO:9 -----	1,2,7,8, 12,14, 16-18, 20,22, 25-30 1,2,7,8, 12,14, 16-18, 20,22, 25-30 1,2,7,8, 12,14, 16-18, 20,22, 25-30

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/30720

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9906426 A	11-02-1999	AU 8685198 A	22-02-1999
		AU 8897898 A	22-02-1999
		EP 1012160 A	28-06-2000
		EP 1009752 A	21-06-2000
		WO 9906428 A	11-02-1999
		US 6117654 A	12-09-2000
WO 0024899 A	04-05-2000	AU 1322700 A	15-05-2000
WO 0017363 A	30-03-2000	AU 6386399 A	10-04-2000
WO 0036108 A	22-06-2000	AU 2178800 A	03-07-2000

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/US 99/30720

Box I Observations wh re c rtain claims were found unsearchabl (Continuation f it m 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,2,7,8,12,14,16-18,20,22,25-30 (partial)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1,2,7,8,12,14,16-18,20,22,25-30 (partially)

An isolated DNA molecule encoding an hIL-Ra1 polypeptide comprising the amino acid residues 37 to 203 of SEQ ID NO:5; said DNA molecule which comprises the nucleic acid sequence of nucleotide positions 118 to 618 of SEQ ID NO:4 or the complete DNA sequence of SEQ ID NO:4; a vector comprising above mentioned DNA molecule; a host cell comprising said vector; an isolated IL-1lp polypeptide encoded by above mentioned nucleic acid molecule; an isolated IL-1lp polypeptide which is an hIL-Ra1 polypeptide comprising the amino acid residues 37 to 203 of SEQ ID NO:5; an antibody which binds specifically to said IL-1lp polypeptide.

2. Claims: 1,2,7,8,11,12,14,16-18,20,22,25-30 (partially)

An isolated DNA molecule encoding an hIL-Ra1 polypeptide comprising the amino acid residues 15 to 193 of SEQ ID NO:7; said DNA molecule which comprises the nucleic acid sequence of nucleotide positions 145 to 681 of SEQ ID NO:6 or the nucleic acid sequence of nucleotide positions 103 to 618 of SEQ ID NO:6 or the complete DNA sequence of SEQ ID NO:6; a vector comprising above mentioned DNA molecule; a host cell comprising said vector; an isolated IL-1lp polypeptide encoded by above mentioned nucleic acid molecule; an isolated IL-1lp polypeptide which is an hIL-Ra1 polypeptide comprising the amino acid residues 15 to 193 of SEQ ID NO:7; an antibody which binds specifically to said IL-1lp polypeptide.

3. Claims: 1,2,7,8,12,14,16-18,20,22,25-30 (partially)

An isolated DNA molecule encoding an hIL-Ra2 polypeptide comprising the amino acid residues 1 to 134 of SEQ ID NO:10; said DNA molecule which comprises the nucleic acid sequence of nucleotide positions 96 to 497 of SEQ ID NO:9 or the complete DNA sequence of SEQ ID NO:9; a vector comprising above mentioned DNA molecule; a host cell comprising said vector; an isolated IL-1lp polypeptide encoded by above mentioned nucleic acid molecule; an isolated IL-1lp polypeptide which is an hIL-Ra2 polypeptide comprising the amino acid residues 1 to 134 of SEQ ID NO:10; an antibody which binds specifically to said IL-1lp polypeptide.

4. Claims: 1,2,5-8,11,12-22,24-30 (partially)

An isolated DNA molecule encoding an hIL-Ra3 polypeptide comprising the amino acid residues 95 to 134 of SEQ ID NO:13; said DNA molecule encoding the hIL-1Ra3 polypeptide comprising the amino acid sequence of amino acid residues 34 to 155 of SEQ ID NO:13 or the amino acid sequence of amino acid residues 2 to 155 of SEQ ID NO:13; said DNA molecule

which comprises the nucleic acid sequence of nucleotide positions 283 to 402 of SEQ ID NO:12 the nucleic acid sequence of nucleotide positions 100 to 465 of SEQ ID NO:12 or the complete DNA sequence of SEQ ID NO:12; an isolated nucleic acid molecule encoding an IL-1lp polypeptide, comprising DNA hybridizing to the complement of nucleotide positions 238 to 465 of SEQ ID NO:12; an isolated Il-1lp polypeptide consisting of an amino acid sequence having at least an 80% sequence identity to the sequence of amino acid residues 95 to 134 of SEQ ID NO:13; an isolated nucleic acid molecule comprising (a) DNA encoding said Il-1lp polypeptide, or (b) the complement of the DNA of (a); a vector comprising above mentioned DNA molecule; a host cell comprising said vector; a process for producing an IL-1lp polypeptide comprising inter alia the step of culturing a host cell comprising said DNA molecule under conditions suitable for expression of the IL-1lp polypeptide; an isolated IL-1lp polypeptide encoded by above mentioned DNA molecule; an isolated IL-1lp polypeptide consisting of an hIL-Ra3 polypeptide comprising the amino acid residues 95 to 134 of SEQ ID NO:13 or the amino acid residues 34 to 155 of SEQ ID NO:13; an antibody which binds specifically to said IL-1lp polypeptide.

5. Claims: 1,2,5-8,12-22,24-30 (partially)

An isolated DNA molecule encoding a mIL-Ra3 polypeptide comprising the amino acid residues 95 to 134 of SEQ ID NO:16; said DNA molecule encoding the mIL-1Ra3 polypeptide comprising the amino acid sequence of amino acid residues 34 to 155 of SEQ ID NO:16 or the amino acid sequence of amino acid residues 2 to 155 of SEQ ID NO:16; said DNA molecule which comprises the nucleic acid sequence of nucleotide positions 427 to 546 of SEQ ID NO:15 or the complete DNA sequence of SEQ ID NO:15; an isolated Il-1lp polypeptide consisting of an amino acid sequence having at least an 80% sequence identity to the sequence of amino acid residues 95 to 134 of SEQ ID NO:16; an isolated nucleic acid molecule comprising (a) DNA encoding said Il-1lp polypeptide, or (b) the complement of the DNA of (a); a vector comprising above mentioned DNA molecule; a host cell comprising said vector; a process for producing an IL-1lp polypeptide comprising inter alia the step of culturing a host cell comprising said DNA molecule under conditions suitable for expression of the IL-1lp polypeptide; an isolated IL-1lp polypeptide encoded by above mentioned DNA molecule; an isolated IL-1lp polypeptide consisting of an mIL-Ra3 polypeptide comprising the amino acid residues 95 to 134 of SEQ ID NO:16 or the amino acid residues 34 to 155 of SEQ ID NO:16; an antibody which binds specifically to said IL-1lp polypeptide.

6. Claims: 1,3,4,7,9,10,13,14,16-18,20,22,24-30 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

An isolated DNA molecule encoding an hIL-Ra1L polypeptide comprising the amino acid residues 26 to 207 of SEQ ID NO:19; said DNA molecule encoding the hIL-1Ra1L polypeptide comprising the amino acid sequence of amino acid residues 1 to 207 of SEQ ID NO:19; said DNA molecule which comprises the nucleic acid sequence of nucleotide positions 79 to 624 of SEQ ID NO:18 or the nucleic acid sequence of nucleotide positions 4 to 624 of SEQ ID NO:18; an isolated nucleic acid molecule encoding an IL-1lp polypeptide, comprising DNA hybridizing to the complememt of the nucleic acid sequence consisting of nucleotide positions 114 to 135 of SEQ ID NO:18; a vector comprising above mentioned DNA molecule; a host cell comprising said vector; an isolated IL-1lp polypeptide encoded by above mentioned DNA molecule; an isolated IL-1lp polypeptide consisting of an hIL-Ra1L polypeptide comprising the amino acid residues 26 to 207 of SEQ ID NO:19 or the amino acid residues 1 to 207 of SEQ ID NO:19; an antibody which binds specifically to said IL-1lp polypeptide.

7. Claims: 1,3,4,7,9,10,14,16,18,20,22,24-30 (partially)

An isolated DNA molecule encoding an hIL-Ra1S polypeptide comprising the amino acid residues 26 to 167 of SEQ ID NO:21; said DNA molecule encoding the hIL-1Ra1S polypeptide comprising the amino acid sequence of amino acid residues 1 to 167 of SEQ ID NO:21; said DNA molecule which comprises the nucleic acid sequence of nucleotide positions 79 to 504 of SEQ ID NO:20 or the nucleic acid sequence of nucleotide positions 4 to 504 of SEQ ID NO:20; a vector comprising above mentioned DNA molecule; a host cell comprising said vector; an isolated IL-1lp polypeptide encoded by above mentioned nucleic acid molecule; an isolated IL-1lp polypeptide consisting of an hIL-Ra1L polypeptide comprising the amino acid residues 26 to 167 of SEQ ID NO:21 or the amino acid residues 1 to 167 of SEQ ID NO:21; an antibody which binds specifically to said IL-1lp polypeptide.

8. Claims: 1,3,4,7,9,10,14-23,25-30 (partially)

An isolated DNA molecule encoding an hIL-Ra1V polypeptide comprising the amino acid residues 46 to 218 of SEQ ID NO:25; said DNA molecule encoding the hIL-1Ra1V polypeptide comprising the amino acid sequence of amino acid residues 1 to 218 of SEQ ID NO:25; said DNA molecule which comprises the nucleic acid sequence of nucleotide positions 208 to 726 of SEQ ID NO:24 or the nucleic acid sequence of nucleotide positions 73 to 726 of SEQ ID NO:24 or the nucleic acid sequence of nucleotide positions 208 to 726 of SEQ ID NO:24; an isolated Il-1lp polypeptide consisting of an amino acid sequence having at least an 80% sequence identity to the sequence of amino acid residues 46 to 218 of SEQ ID NO:25; an isolated nucleic acid molecule comprising (a) DNA

encoding said Il-1lp polypeptide, or (b) the complement of the DNA of (a); a vector comprising above mentioned DNA molecule; a host cell comprising said vector; a process for producing an IL-1lp polypeptide comprising inter alia the step of culturing a host cell comprising said DNA molecule under conditions suitable for expression of the IL-1lp polypeptide; an isolated IL-1lp polypeptide encoded by above mentioned nucleic acid molecule; an isolated IL-1lp polypeptide consisting of an hIL-Ra1V polypeptide comprising the amino acid residues 46 to 218 of SEQ ID NO:25; an antibody which binds specifically to said IL-1lp polypeptide.

PATENT COOPERATION TREATY

REC'D 29 MAY 2001
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SMK/FP5865621		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/30720	22/12/1999	23/12/1998
International Patent Classification (IPC) or national classification and IPC C12N15/25		
Applicant GENENTECH, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/07/2000	23.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Giebeler, K Telephone No. +49 89 2399 8546

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/30720

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1,2,4-82,85-91,94, 96-113	as originally filed			
3,83,84,92,93, 95	as received on	21/07/2000	with letter of	21/07/2000

Claims, No.:

1-30	as originally filed

Drawings, sheets:

1/24-24/24	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 3-6, 9-11,13,15,19,21,23,24 (all completely); 1,2,7,8,12,14,16-18,20,22,25-30 (all partially).

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 3-6,9-11,13,15,19,21,23,24 (all completely); 1,2,7,8,12,14,16-18,20,22,25-30 (all partially).

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.
   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2,7,8,12,14,16-18,20,22,25-30 (all partially)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1,2,7,8,12,14,16-18,20,22,25-30 (all partially)
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1,2,7,8,12,14,16-18,20,22,25-30 (all partially)
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the opinion

1. The amendments on pages 3 and 83 have been disregarded because they are considered to go beyond the content of the application as originally filed. In the letter of 21/07/00, the Applicant has merely asserted that the EST in question was publicly available, without providing documentary evidence showing that the newly introduced information was known from the prior art.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

2. This opinion has only been established for the subject-matter searched, i.e. invention number 1 as defined in the international search report.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. The following documents are cited:

   D1: DINARELLO C. A. ET AL.: ' SEMINARS IN ONCOLOGY, vol. 24, no. 3, Suppl. 9, June 1997 (1997-06), pages S9-81-S9-93
   D2: WO 99 06426 A

4. The current assessment is based on the assumption that the claims enjoy priority rights from the filing date of the priority document on 23.12.98. If it later turns out that this is not correct, the document D2 cited in the international search report could become relevant.

5. The subject-matter of claims 1, 2, 7, 8, 12, 14, 16-18, 20, 22 and 25-30 as far as it relates to the DNA molecule of Figure 2 encoding the polypeptide designated "hIL-1Ra1" (SEQ ID NO:5) is considered to be based on an inventive step.
The document D1 disclosing the protein hIL-1Ra appears to represent the closest prior art document. The protein "hIL-1Ra1" according to the application is distinguished therefrom in that it (i) does **not** bind to the human IL-1 receptor (hIL-1R) and (ii) does bind to the human IL-18 receptor (hIL-18R), as evidenced by Example 9, pages 89/90 of the application.
The technical problem is thus seen in the provision of a protein binding to hIL-18R and not binding to hIL-1R. The solution as provided with the claimed "hIL-1Ra1" protein was not obvious from the available prior art. It could not be expected that searching an EST DNA database with the human IL-1Ra sequence would result in the claimed protein which solves the problem posed.

Re Item VI
Certain documents cited

6. Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99 06426	11.02.99	03.08.98	04.08.97 02.07.98
WO 00 24899	04.05.00	27.10.99	27.10.98
WO 00 17363	30.03.00	17.09.99	18.09.98

Re Item VIII
Certain observations on the international application

7. The term "about" used in claims 1, 2, 7, 8 and 22 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers,

thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

8. Claims 22 and 25 comprise all the features of claim 20 and are therefore not appropriately formulated as claims dependent on the latter (Rule 6.4 PCT). The same applies to claim 14 which comprises all the features of claim 1.